of Collombat et al. demonstrate that Pax4 alone is sufficient to overcome this block and raise the possibility that deficiency of glucagon or glucagon signaling may serve as a cue for the regeneration of both the alpha cells and duct-associated progenitor cells.

In the transgenic mouse model studied by Collombat et al., the dramatic expansion of the beta cell mass throughout postnatal life is attributed to a continuous formation of beta cells through alpha cell reprogramming rather than the slow self-replication of pre-existing mature beta cells (Dor et al., 2004). These observations provide proof that the adult pancreas has latent capabilities to regenerate new beta cells in response to injury and do so by resurrecting developmental programs to allow amplification of progenitor cells and selective lineage commitments. In this case, the beta cells originating from cells that express glucagon are fully functional and counter diabetes induced by streptozocin. This study will redirect thinking in the field of regenerative medicine in the treatment of diabetes, which has been focused on the premise that beta cell neogenesis only occurs through the replication of existing beta cells (Dor et al., 2004).

Finally, these studies show that replacement of endocrine tissue by transplantation of insulin-producing cells, derived from embryonic stem cells or other cells, is not the only feasible approach to a permanent treatment for diabetes. To the contrary, it is now possible to contemplate treatment approaches that coax pre-existing, latent stem/progenitor cells and alpha cells to make new beta cells.

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Data Harvesting from Fields of Spindles

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The mitotic spindle is essential for chromosome segregation and must be large enough to accommodate all of the chromatin in the dividing cell. In this issue, Dinarina et al. (2009) grow "fields" of spindles on coverslips to investigate the relationship between chromatin and spindle size as well as intrinsic mechanisms of spindle assembly.

The main function of the mitotic spindle is to accurately segregate replicated chromosomes during cell division. Spindle size varies little between cells of the same type but does not always scale with cellular dimensions. This point is strikingly illustrated by the amphibian egg during meiosis when the diameter of the egg is roughly 30 times longer than the length of the spindle. Thus, the steady-state dimensions of the spindle are not always constrained by the geometry of the cell and must instead be determined by intrinsic mechanisms. In this issue of *Cell*, Dinarina et al. (2009) use an innovative approach involving growing "fields" of spindles in *Xenopus* extracts to examine the role of chromatin in modulating spindle assembly and size.

How is spindle size set? In order to ensure genomic fidelity during cell division, a spindle must be large enough to attach to, align, and segregate all of the chromosomes within the cell. This suggests that spindle size should scale with the amount of chromatin or at least with the area that it occupies on the metaphase plate. One way to achieve this proportionality is for chromatin to dictate where and to what extent the microtubules that make up the spindle will polymerize. Indeed, it is now known that spindle microtubules form locally in response to at least two chromatin-based signaling pathways (Kalab et al., 1999; Sampath et al., 2004).

The determination of spindle size is also a mechanical problem that requires consideration of the forces generated by the dynamics of microtubule polymerization/depolymerization and by the motors that move along microtubules using them

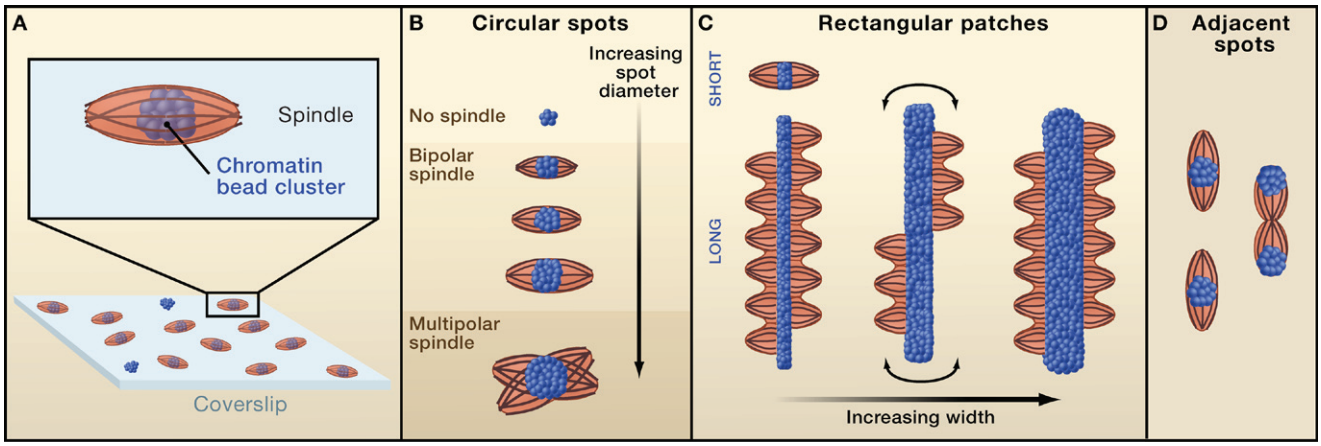

Figure 1. Modulating Spindle Assembly and Size

Microcontact printing on coverslips produces a range of patterns into which chromatin-coated beads can be deposited to enable investigation of spindle assembly from microtubules in *Xenopus* egg extracts.

(A) On printed coverslips, arrays of spindles (brown) form around chromatin bead clusters (blue).

(B) Circular bead clusters of increasing diameter reveal a chromatin size threshold. Above this threshold, nonfunctional multipolar spindles are generated instead of functional bipolar spindles.

(C) In contrast to previously published results (Gaetz et al., 2006), rectangular bead patches (lines) induce a spindle transition from bipolar to multipolar as chromatin length increases. Wider lines produce asymmetric multipolar structures that flip dynamically from one side of chromatin to the other by as yet unknown mechanisms. These structures revert to "symmetric" arrays when the line width is further increased.

(D) Interaction between adjacent spindles results in the formation of aberrant structures. These interactions are dependent on the motor dynein and seem to dominate over other forces that orient the spindle with respect to chromatin or that maintain separation between the spindle poles.

as tracks. These forces move, slide, and align microtubules to form the characteristic fusiform shape of the spindle and to set its length (Desai, 2002). Within each half of the spindle, intrinsically polar microtubules, each with a dynamic plus end and a more stable minus end, are eventually oriented parallel to the interpolar axis with their minus ends pointing toward the pole. This architectural arrangement provides a means for motors with opposite directionalities (that is, either plus end- or minus end-directed motors) to work against each other to modulate spindle length. This antagonism is the basis of force-balance models for spindle length determination (Mogilner et al., 2006).

To tackle multiple facets of the problem of how spindle size is determined, Dinarina and colleagues created fields of spindles in vitro. They deposited arrays of chromatin-coated bead clusters on otherwise inert coverslip surfaces using microcontact printing. Aggregates of these same beads are sufficient to initiate spindle assembly when added in suspension to extracts of *Xenopus* eggs arrested in stage II of meiosis, typically generating spindles with lengths of ~35 μm (Heald et al., 1996). When the coverslip-affixed beads are covered with frog egg extract, bipolar microtubule structures assemble around most clusters, creating arrays of spindles on the coverslip surfaces (Figure 1A). Flexibility in the design of the microcontact stamp that prints the pattern for the bead clusters allows the investigators to vary the size, geometry, spacing, and DNA content of the bead patterns. By keeping the DNA density constant and varying the size of the circular spots of bead clusters, the authors uncover a linear relationship between chromatin size and spindle dimensions. However, when the cluster diameter is increased beyond a certain size, a greater proportion of assembled structures lose the bipolar symmetry required to properly segregate chromosomes and instead become multipolar (Figure 1B). Intriguingly, increasing the chromatin density (up to 4-fold) while keeping its area constant has only a modest effect on spindle size.

These results have important implications for models of spindle assembly that rely on the size of the signaling gradients emanating from chromatin. There is no doubt that such signals are present and are required for spindle formation and assembly (Kalab et al., 2006). However, there is no direct evidence, to our knowledge, that the dimensions of the gradient affect spindle size. The authors argue convincingly that the critical parameter dictating spindle size is likely to be the surface area of chromatin and not its mass. Indeed, they point out that chromatin-based stabilization of microtubules (via the small GTPase Ran) is initiated on the surface of chromatin. However, whether bead clusters harboring higher chromatin loads generate more diffusible signal than bead clusters of the same size with less chromatin has not yet been tested. A telltale experiment would be to compare in real time the shapes of Ran-dependent signaling gradients that form around bead clusters of similar size but with different chromatin loads. If gradient dimensions have any functional consequences with respect to spindle size, Dinarina et al.'s interpretation predicts that the gradient in each case should be roughly the same size.

Dinarina and colleagues further explore the bipolar-to-multipolar transition observed for circular chromatin spots in experiments where the geometry of the bead is changed to rectangular patches or "lines." They find that shorter chromatin lines support normal bipolar spindle assembly, whereas longer chromatin lines of the same thickness are decorated along their entire length

and on both sides by a multipolar microtubule array (Figure 1C). The authors contend that in the latter case, although spindle microtubules associate with all of the chromatin, the multipolar and disorganized nature of the spindle structure would not be able to function properly to segregate chromosomes. Therefore, at a critical chromatin size, the same bipolar-to-multipolar transition that occurs for circular chromatin spots also occurs for rectangular patches. These results imply that a bipolar spindle has a limited segregation capacity that is determined by its ability to minimize the space occupied by its chromosomes (which, unlike beads affixed to a rigid surface, are free to move around). This implication explains the observation in frog egg extracts that pairs of juxtaposed spindles fuse into a single bipolar spindle, but fusion of more than two spindles often results in disorganized multipolar structures (Gatlin et al., 2009; Sawin and Mitchison, 1991). However, the fact that different cell types within the same organism have spindles of markedly different sizes suggests that the relationship between segregation capacity and spindle size must vary from one cell type to the next and that some cells are more efficient at packaging the same amount of chromatin into a smaller space.

In a demonstration of the broader utility of the micropattern approach, Dinarina et al. use the same spindle arrays to investigate intrinsic mechanisms of spindle assembly. Spindles assembled around small rectangular chromatin bead clusters are typically oriented with their interpolar axes lying perpendicular to the long axis of the chromatin. The authors find that these structures can be rotated away from their preferred axis by dynein-dependent traction forces between the poles of proximal spindles. These same pole-to-pole forces also promote the assembly of asymmetric half-spindles (Figure 1D). This demonstrates that interactions between adjacent spindles can perturb the normal mechanics that govern the assembly of individual spindles by providing a spatial configuration that allows polar traction forces to dominate. This finding may lend credence to force-balance models of spindle assembly.

The flexibility of the micropattern design system, coupled with the biochemical tractability of *Xenopus* egg extracts, should allow exploration of how specific proteins contribute to spindle assembly. Furthermore, this approach generates robust datasets that are well suited to the development of new models of spindle assembly and that provide a means to better test existing models. Needless to say, it will be interesting to see what bounty future harvests of spindle fields will yield.

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DNA Makes RNA Makes Innate Immunity

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Microbial DNA in the cytosol induces production of interferon-β (IFN-β) and an innate immune response. Chiu et al. (2009) now implicate cytosolic DNA-dependent RNA polymerase III as the DNA sensor linking DNA release by pathogenic bacteria and viruses in the host cell cytosol to IFN-β production and innate immunity.

DNA can be dangerous, particularly if it is in the wrong place. Accumulation of foreign DNA or self-DNA in the cytosol triggers an inflammatory response with the release of cytokines, such as interleukin-1β (IL-1β) and interferon-β (IFN-β). In the case of foreign DNA, this inflammatory response is important for innate immunity and host defense against bacterial and viral pathogens. An inflammatory response associated with self-DNA has been implicated in autoimmune diseases, such as systemic lupus erythematosus (SLE). Interestingly, this role for cytosolic DNA in inflammation was identified well before DNA's role in transcription was appreciated. In his Nobel Prize acceptance speech in 1908,